Immunology assignment 2

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1- Complement system:

The complement **is a group of serum proteins that circulate in an inactive state. A variety of specific and non-specific immunologic mechanisms can convert the inactive form of complement proteins into an active form leading to lysis of bacteria, cells and viruses**;

- ***The complement system includes serum and membrane-bound proteins that functions in both natural and acquired defense system.***
- **The term 'complement' refers to the ability of these proteins, to complement (augment) the effects of other components of the immune system (e.g. antibody).**

Complement has several main effects:

1. Lysis of cells (e.g. bacteria, tumor cells and enveloped virus directly).
2. Production of peptide fragments that participate in inflammation and attract phagocytes.
3. Opsonization of organisms and immune complexes for clearance by phagocytosis and enhancement of antibody-mediated immune responses.

- Activation of the complement system can be initiated, either by antigenantibody complexes or by a variety of non-immunological molecules.

The Complement Pathways

The complement system **works as a cascade.** A cascade is a set of reactions that amplify some effects, i.e. more products are formed in the second reaction than the first, still more in the third and so on. Of the proteins, so **far identified in the complement system, 13 participate in the cascade itself, seven activate or inhibit reactions in the cascade**. The components of the classical pathway are numbered from C1 to C9 and the reaction sequence is C1-C4-C2-C3-C5-C6-C7- C8-C9. **Up to C5, activation involves proteolytic cleavage,** liberating smaller fragments from C2 through C5 except for C2, where for historical reasons **the larger fragment that remains bound to the complex is termed C2a,** the **smaller fragments are by the letter 'a' (e.g. C4a) and the larger fragments by letter 'b' (e.g. C5b).**

- **Activation of the complement system can be initiated, either by antigen antibody complexes or by a variety of non-immunological molecules**.

Sequential activation of complement components occurs via three main pathways.

1-The Classical Pathway

1**. C1, which binds to the Fc region of an immunoglobulin, is composed of three proteins**: C1q, C1r, and C1s. C1q is an aggregate of polypeptides that bind to the Fc portion of IgG and IgM.

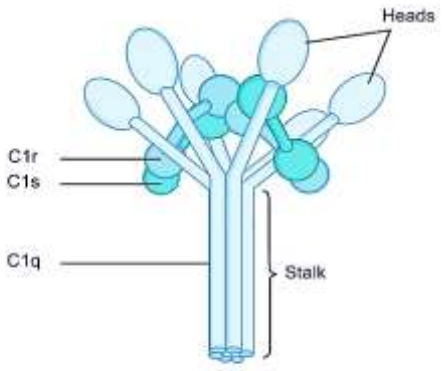
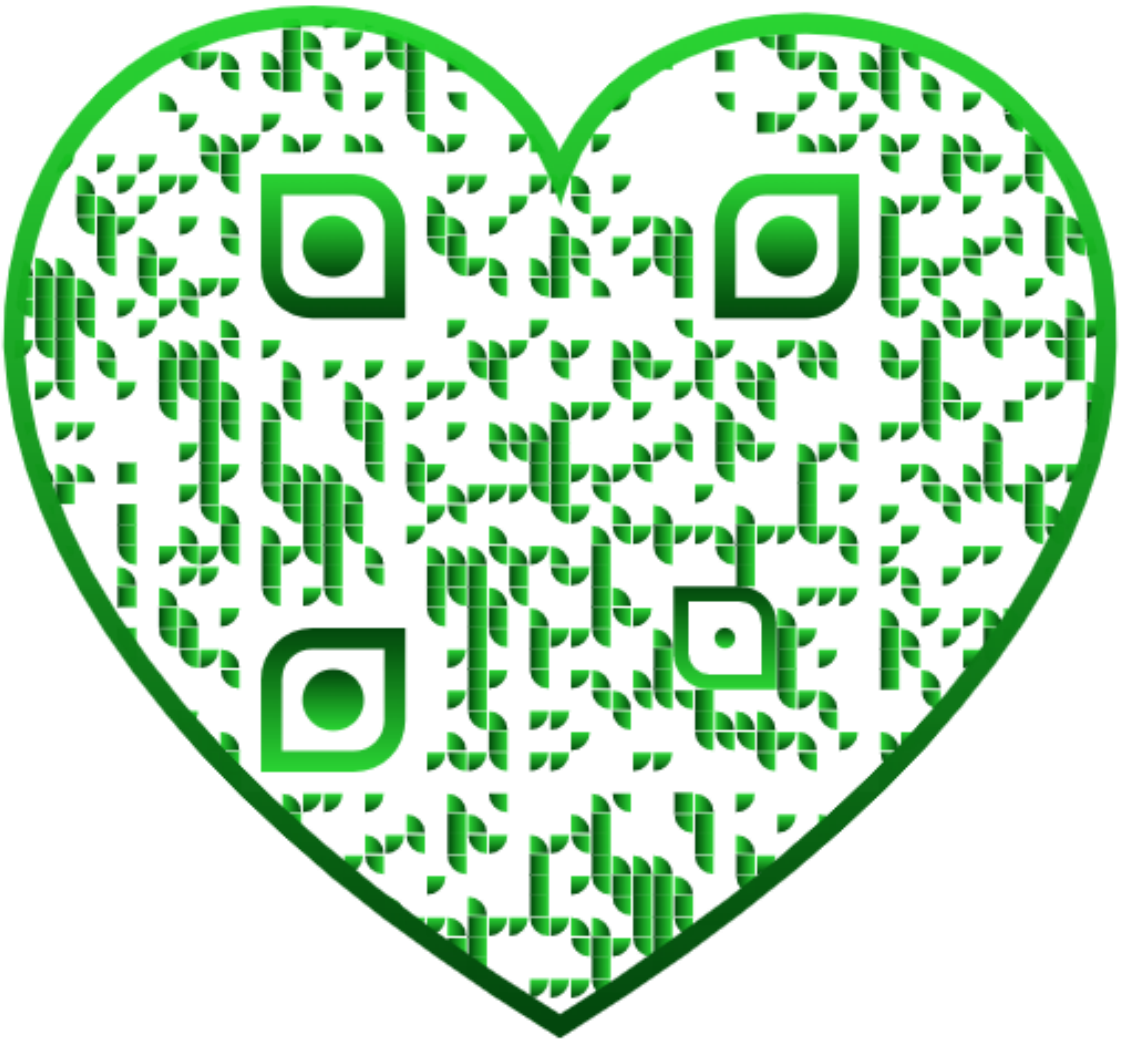


Fig. 7.1: C1 macromolecular complex consisting of C1q and two molecules of each C1r and C1s ($(1qr_2s_2)$)

2. The antibody–antigen immune complex bound to C1 activates C1s, which cleaves C4 and C2 to form C4b2b.



3. The latter protein (C4b2b) is an active C3 convertase, which splits C3 molecules into two fragments: C3a and C3b. As mentioned earlier, C3a is a potent anaphylatoxin.
4. C3b forms a complex with C4b2b, producing a new enzyme, C5 convertase, which cleaves C5 to form C5a and C5b.
5. C5b is now available to bind to C6 and C7 and form the C5b/C6/C7 complex.
6. Finally, C9 binds to this newly formed complex to produce the formation of the membrane attack complex (MAC). Once the MAC is formed, cell lysis ensues shortly thereafter.

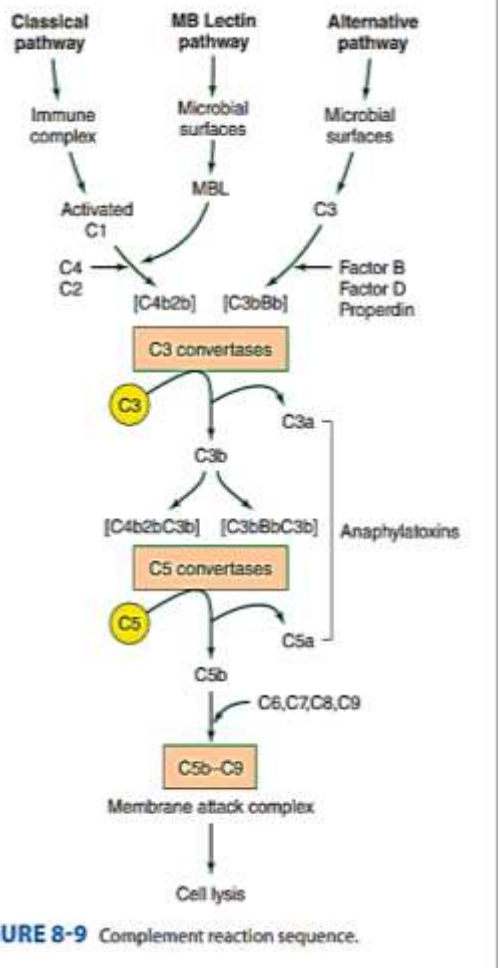


FIGURE 8-9 Complement reaction sequence.

- Only IgM and IgG fix complement via the classic pathway. Furthermore, only IgG subclass 1, 2, and 3 fix complement whereas IgG4 does not.

♦ **An example of the classical complement pathway in action can be observed in herpes simplex virus (HSV) infections**. HSV replication within cells is accompanied by the insertion of virus proteins into the cell surface membrane. A specific anti-HSV antibody can bind to the surface of the infected cell by its Fab site. **The Fc portion of the antigen– antibody complex is now exposed and ready for C1 to attach.**

2- The Alternative Pathway

1**. The alternative pathway of complement can be activated by infectious agents** that activate the complement system by triggering the cellular production of factors B, D, and proper din.
2. These factors cleave C3 and generate C3 convertase. C3 convertase (C3bBb) that was generated during the alternative pathway produces more C3b.
3. The additional C3b binds to the C3 convertase to form C3bBbC3b. This enzyme is the alternative pathway C5 convertase that generates C5b, leading to production of the MAC described earlier.

3- Mannose-Binding Lectin Pathway

1. The lectin pathway is an important component of the innate immune response and is similar to the classical pathway at the point of cleavage of C4. However, the major difference is that it is initiated by the binding of mannose-binding lectin (MBL) to polysaccharides on bacterial surfaces.
2. The binding of MBL to a pathogen results in the formation of a tricomplex of MBL with two serine proteases (MASP-1 and MASP-2).
3. This tricomplex is now activated to cleave C4 into C4a and C4b and C2 into C2a and C2b. The new complex C4bC2a is a C3 convertase and proceeds to cascade as the classic pathway.

2- Interferons and its medical uses.

Interferons: are critical cytokines that play a key role in defense against virus infections and other intracellular organisms, such as Toxoplasma gondii. And its proteins that are currently grouped into three families: IFN-`, IFN-a, and IFN-f.

- **The IFN-α and IFN-β families constitute type I IFNs,** i.e., acid-stable proteins that bind to the same receptor on target cells and usually induced by virus infections, with leukocytes producing IFN-α. Fibroblasts and epithelial cells produce IFN-β.
- **IFN-γ, a type II IFN**, is acid-labile and binds to a separate receptor on target cells and usually the product of activated T lymphocytes.

♦ **IFNs interact with cell receptors to produce a wide variety of effects** that depend on the cell and IFN types.

- IFNs, particularly IFN-γ, display immune-enhancing properties, which include increased antigen presentation and macrophage, NK cell, and cytotoxic T-lymphocyte activation.

- IFNs also inhibit cell proliferation. In this respect, IFN-α and IFN-β are more potent than IFN-γ.

- Another striking IFN action is increased expression of MHC molecules on cell surfaces While all three types of IFN induce MHC class I molecules, only IFN-γ induces class II expression.

♦ *In glial cells, IFN-β antagonizes this effect and may, in fact, decrease antigen presentation within the nervous system.*

♦ IFN-α is approved for the treatment of several neoplasms, including hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, and Kaposi's sarcoma, and for treatment of hepatitis B and C infections. It has also shown activity as an anti-cancer agent in renal cell carcinoma, carcinoid syndrome, and T-cell leukemia, IFN-β is approved for use in relapsing-type multiple sclerosis.

♦ IFN-γ is approved for the treatment of chronic granulomatous disease and IL-2, for metastatic renal cell carcinoma and malignant melanoma.

♦ Clinical investigations of other cytokines, including IL-1, -3, -4, -6, -10, -11, and -12, are ongoing. Toxicities of IFNs, which include fever, chills, malaise, myalgias, myelosuppression, headache, and depression, can severely restrict their clinical use.

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Reverences:

1- Jawetz, Melnick, & Adelberg's Medical Microbiology Twenty-Eighth Edition CHAPTER 8.

2- G. Katzung Basic & Clinical Pharmacology Fourteenth Edition CHAPTER 55 .

3- Sunil Kumar Mohanty Textbook of Immunology Second Edition chapter 7.

III Mr. Rezg